

Control of Cell Division Patterns in Developing Shoots and Flowers of *Arabidopsis thaliana*

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Development of flowering plants is different from that of the animal model systems. In flowering plants such as *Arabidopsis*, embryogenesis serves primarily to establish the shoot and root apical meristems, which later develop into the mature plant. Most morphogenesis and pattern formation thus occur postembryonically. The shoot apical meristem (SAM), which is a small collection of undifferentiated cells, first forms and then arrests during embryogenesis; after seed germination, it activates and becomes the source of the cells that will later make up the entire above-ground part of the plant (Steeves and Sussex 1989; Meyerowitz 1997). The morphogenetic activities of the SAM after seed germination consist of a small number of stereotyped programs, with the environment playing an important part in which programs are selected. This allows the plant to respond continually to changes in its environment by altering its growth and development, rather than responding as do most animals by activities of brain and muscles. The fundamental programs followed by the *Arabidopsis* SAM, in addition to maintenance (which allows the meristem to serve as a continuing population of stem cells), are either production on its flanks of leaves with axillary secondary SAMs or production of flowers (Fig. 1A,B,C). A secondary SAM can behave as the primary SAM, making third-order meristems or flowers, or it can be held in a state of developmental arrest. These simple sets of meristematic choices thus provide a tool kit for plant architecture, and the choice made at any time by each meristem sums to the total form of the plant.

Little is known about the control of pattern formation in SAMs and their derivatives, but one thing is clear: It depends very directly on control of planes and numbers of cell divisions. This can be inferred from the small number of processes available for plant morphogenesis. There is no cell migration in meristems, nor any slippage of cells relative to one another, as the cells are encased in a cellulose-based wall. Although plants use programmed cell death for many things, it does not appear that they use it to regulate the number of cells in meristems. Instead, it is used to make dead structures, such as xylem or autumn leaves, or as a local response to pathogens. Without migration, slippage, or cell death to regulate cell number and cell position in meristems, only highly regulated cell division is left.

Beyond inference, there is much direct evidence of tight control of planes and numbers of cell divisions in

SAMs. Even in the embryo, an *Arabidopsis* SAM has three distinct cell layers, which remain clonally distinct through the life of the plant, by continued anticlinal division in the outer two layers (Fig. 1D). The L1 layer is on the surface and is ancestral to the epidermal cell layer of the shoots, leaves, and flowers. The L2 layer is directly beneath the L1 layer; its derivatives are the subepidermal cells of stems, leaves, and floral organs. In addition to the anticlinal divisions that maintain this layer, the development of leaves and floral organs involves regulated periclinal divisions of L2 cells, so that in a mature organ, L2 derivatives can provide several layers of cells. Among the L2 derivatives are the germ cells, found in pollen grains and ovules. The L3, or corpus, is not a single cell layer, but a collection of cells in which divisions occur in all planes. The corpus derivatives include the pith and vasculature of the stem and the most central cells of leaves and floral organs.

In addition to this layering, which is well demonstrated in many plants by experiments with genetic mosaics (Tilney-Bassett 1986), observations of cell division patterns and cellular morphology in SAMs show that the meristem is divided in a different way, into domains of cell division activity that cut across the clonal boundaries (see Fig. 1C). The central zone is at the meristematic tip and consists of slowly dividing, relatively inactive cells. Surrounding the central zone is the peripheral zone, consisting of metabolically active and rapidly dividing cells. It is cell divisions in the peripheral zone that establish the leaf/shoot or floral units that develop on the meristematic flanks. The core of the meristem is the rib meristem, which has its own cell division rate and pattern, making long lines of cells that are the lineages contributing to stem growth (Steeves and Sussex 1989; Meyerowitz 1997).

The maintenance of meristem structure and shape throughout the life of a plant and the formation of structures with characteristic positions, shapes, and sizes, such as leaves and floral organs, also demonstrate a very tight and regulated control of cell division (and cell elongation) patterns. Furthermore, the coordinated growth of the clonal layers and demonstrations that reduction in cell division rates in one layer are accommodated by increased cellular proliferation in other layers (Tilney-Bassett 1986) indicate that cells in different meristematic regions communicate cell division information to each other. We

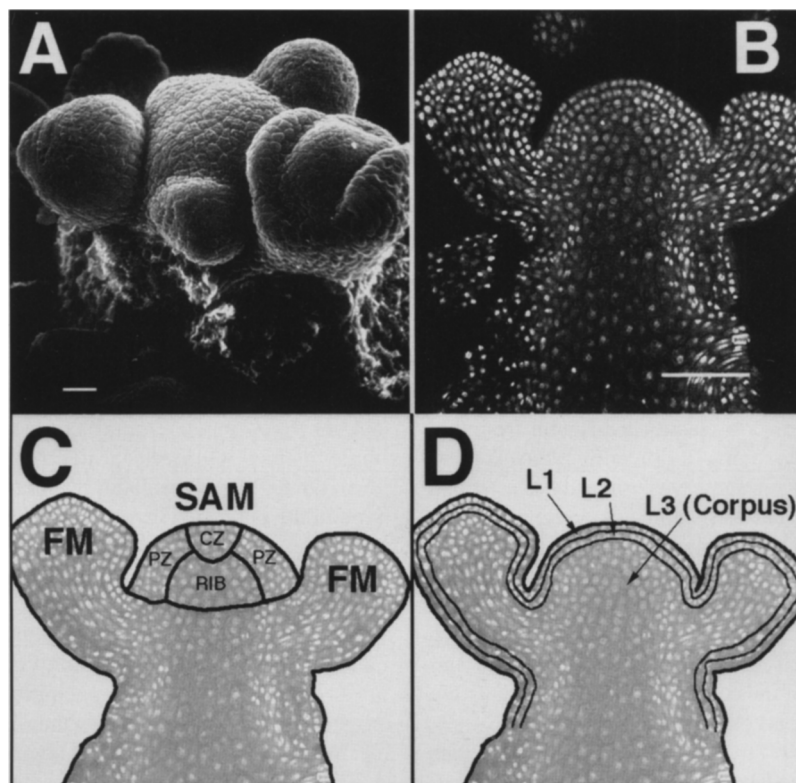


Figure 1. Shoot apical meristem structure. (A) Scanning electron micrograph of an *Arabidopsis thaliana* (Landsberg *erecta* wild-type) SAM, surrounded by secondary meristems (which will develop into flowers). Bar, 10 μ m. (B) Laser confocal microscope optical section through an apex similar to that in A, but from ecotype Ws-0. Nuclei were stained with propidium iodide. Bar, 50 μ m. (C) Same apex shown in B, but with different meristems and meristematic regions labeled. (SAM) Shoot apical meristem; (FM) floral meristem; (CZ) central zone; (PZ) peripheral zone; (RIB) rib meristem zone. (D) The same apex as in B and C, this time labeled to show the clonal layers.

do not know how meristem cells send or receive cell division information. Finding out will illuminate the basic processes of plant development and also allow experimental control of plant form.

My laboratory has taken a genetic approach toward finding how meristematic cells communicate cell division information, by inducing mutations and collecting mutant lines in which the usual regulated pattern of cell divisions in meristems has become abnormal. One sensitive indicator of changes in meristematic cell division pattern is change in floral organ number. *Arabidopsis* flowers derive from floral meristems, which are products of SAMs but are not themselves like shoot apical meristems, in that they make a different set of organs and are determinate in their growth pattern (Smyth et al. 1990). Nonetheless, many genes that regulate patterns and numbers of cell divisions in SAMs also appear to be important in cell division control in floral meristems; in floral meristems, extra cells result in extra floral organs, whereas reduced cell number in floral meristems results in reduced numbers or absence of floral organs (Koornneef et al. 1983; Clark et al. 1993, 1995, 1996; Laux et al. 1996). Changes in the numbers of floral organs are easily detected in mutant screens and lend themselves to quantitation by counting of organs. They thus serve as a convenient phenotype by which to find mutations affecting

the regulation of meristematic cell divisions. Although it is equally easy to screen for mutations with reduced or extra floral organs, we have concentrated on extra organ mutants because these cannot be explained by the trivial possibility that the plants are simply unable to make cellular components such as cell wall, or are improperly nourished.

RESULTS AND DISCUSSION

The first extra-organ mutations that we studied in detail were recessive and semidominant alleles of *CLAVATA1* (*CLV1*, Leyser and Fumier 1992; Clark et al. 1993; Crone and Lord 1993). Loss-of-function mutations in *CLV1* cause progressive enlargement of the shoot apical meristem during plant growth. In mature *clv1* embryos, the SAM is slightly larger than normal; it becomes progressively larger as postgermination growth occurs. This results in increasing thickness of the main stem with time, sometimes proceeding to grossly abnormal, fasciated forms, and loss of the usual phyllotactic pattern of leaves and secondary meristems. Secondary and higher-order SAMs are similarly affected, and floral meristems are larger than normal (because they have extra cells) from early stages. Wild-type floral meristems at a stage before the primordia of the inner floral organs have

formed (stage 3; Smyth et al. 1990) are flattened domes, with a diameter of approximately 50 μm and a height of approximately 12 μm . Floral meristems of homozygotes for a strong *clv1* mutant allele like *clv1-4* average about 70 μm in diameter and 40 μm in height, with the same cell size as in wild type. The consequence of this for flowers is that each flower has many extra organs. A wild-type *Arabidopsis* flower has four sepals, four petals, six stamens, and a compound ovary made of two fused carpels. Flowers of a line homozygous for *clv1-4* may average five or six sepals, five petals, nine or ten stamens, and have ovaries of four to six carpels. *clv1* mutations also cause continued cell division in the center of developing flowers, beyond the stage when such cell division would ordinarily stop. This causes extra ovaries to form within the fourth whorl ovary, in a Russian-doll type of arrangement. This slight loss of determinacy is greatly exaggerated in double-mutant combinations with genes that are required for floral determinacy, such as *AGAMOUS* (*AG*; Yanofsky et al. 1990). *ag-2 clv1-4* double-mutant floral meristems, for example, can fasciate and grow to enormous sizes, all the while making endless whorls of floral organs (Clark et al. 1993; Meyerowitz 1997).

The phenotypes of *clv1* mutants point to several possible models for the action of the gene. One prominent possibility is that the gene is involved in the cell-cell signaling that regulates the number of cell divisions in shoot and floral meristems and that the wild-type function of the gene is to act in the reception and interpretation of cell division signals. Loss-of-function alleles cause extra cell division, so the normal function of the gene would be to repress excess meristematic cell divisions.

To clarify the biochemical function of *CLV1*, we cloned the gene by chromosome walking (Clark et al. 1997). It codes for an apparent transmembrane receptor kinase. The encoded protein has at its amino-terminal end a potential signal peptide, followed by a putative extracellular domain of 21 complete leucine-rich repeats. This is followed by what is likely to be a transmembrane domain. The putative intracellular domain has all of the residues found conserved among serine/threonine protein kinases. Consistent with this, the putative kinase domain, as expressed in an *Escherichia coli* protein expression system, shows protein kinase activity, autophosphorylating on serine (Williams et al. 1997).

As leucine-rich repeats are well-characterized protein-binding motifs (Buchanan and Gay 1996), it would appear that the *CLAVATA1* protein binds an extracellular protein or peptide ligand, with binding activating a Ser/Thr protein kinase, and through a signal transduction cascade, repressing certain meristematic cell divisions. In situ hybridization with an antisense probe complementary to a non-cross-hybridizing portion of the *CLV1* RNA shows that the RNA is present in both shoot and floral meristems. Expression is seen at least as early as mature seeds in the shoot apical meristem (H. Sakai and E.M. Meyerowitz, unpubl.), and in postgermination plants, the shoot apical meristem shows *CLV1* RNA in a region that approximately corresponds to the rib meristem (Clark et al. 1997). If it is true that *CLV1* acts in the cells where its

RNA is expressed, then the *CLV1* mutant phenotype is in part nonautonomous: Loss-of-function mutations in *CLV1* cause enlargement of the entire shoot apical meristem, including all three clonal layers. In situ hybridization does not detect *CLV1* RNA in the L1, and probably not in the L2 layer, although in *clv1* mutants, the layered nature of the meristem is not disrupted. Thus, excess cell division in the deeper cells of the meristem seems to activate comparable excess division in the L1 and L2 layers, indicating that there is communication of cell division information between meristematic cells. A reasonable speculation would be that *CLV1* is involved in such communication, as a receptor in rib meristem cells.

One can then ask what might be some of the other components of the meristematic communication system. The products of other genes with mutant phenotypes similar to those of *clv1* are clear candidates. We have studied one such gene in some detail; it is called *CLAVATA3* (Fig. 2) (Alvarez and Smyth 1994; Clark et al. 1995). The mutant phenotypes of the weaker *clv3-1* and stronger *clv3-2* alleles are identical to those of *clv1* alleles—extra cells in the SAM of the mature embryo, increasing cell number and size of the SAM throughout the life of the plant, stem thickening and occasional stem fasciation, and floral meristems with extra cells, leading to flowers with excess numbers of organs, and nested ovaries. *CLV1* maps to the first chromosome of *Arabidopsis*, whereas *CLV3* maps to chromosome 2, so the mutations in *clv1* and *clv3* are clearly not allelic. Nonetheless, doubly heterozygous plants (*clv1/+*; *clv3/+*) show a mutant phenotype of somewhat enlarged SAM and extra floral organs. This nonallelic noncomplementation is one indicator that the products of the two genes may act in the same or in closely related pathways: Reduction in the level of one protein sensitizes the plant to a reduction in the level of the other (Clark et al. 1995). Another indicator that *CLV3* may act in the pathway defined by *CLV1* is the phenotype of plants homozygous for loss-of-function alleles in both genes. Double homozygotes (*clv1/clv1*; *clv3/clv3*) have the same phenotype as either single homozygote; formally, that is, *clv1* is epistatic to *clv3*, and *clv3* is epistatic to *clv1*. This is what would be expected if recessive alleles of each eliminate a signal transduction pathway, and the proteins coded by each gene act in different steps in the same pathway (Clark et al. 1995).

From these data, it is not possible to assign a role to *CLV3* in the pathway, although an appealing possibility is that *CLV3* codes for the *CLV1* ligand (Fig. 3). It could just as easily be true though that *CLV3* codes for a cytoplasmic or nuclear protein that responds to *CLV1* activation. We are in the process of trying to obtain molecular clones of *CLV3*, but there is as yet no clue to the nature of the encoded protein.

Given that *CLV1* and *CLV3* seem to be acting in the same pathway, can any additional gene products that act in this pathway be identified? One prominent possibility for an additional component is KAPP, a kinase-associated protein phosphatase identified by Walker and his colleagues (Stone et al. 1994). KAPP associates with the kinase domain of RLK5, an *Arabidopsis* leucine-rich re-

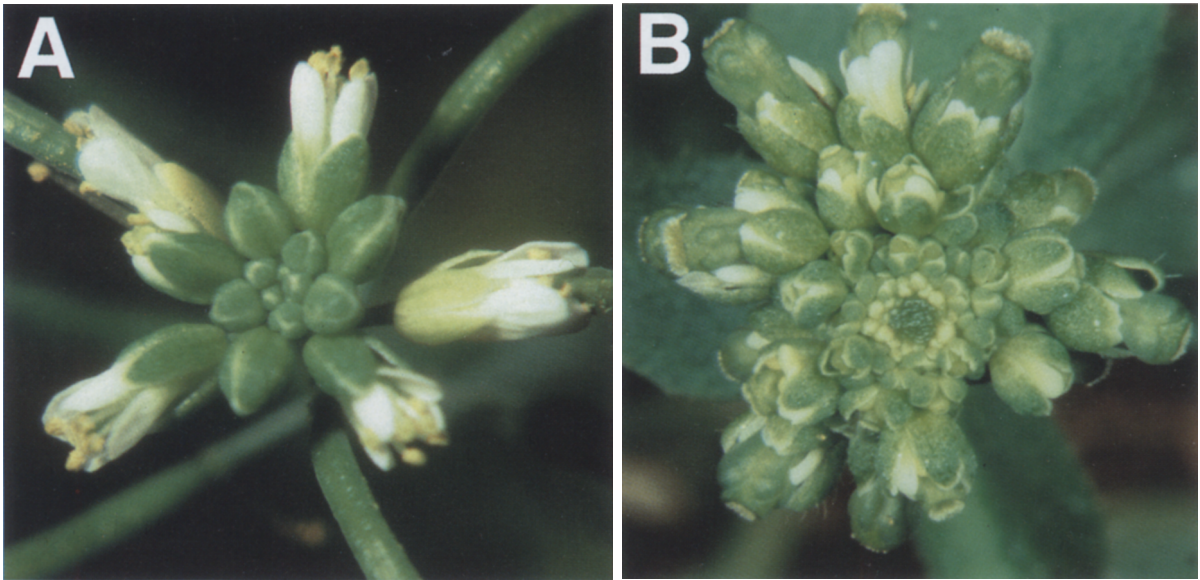


Figure 2. Wild-type and *clavata3-2* mutant inflorescence apices. (A) Wild-type inflorescence apex viewed from above. The spiral phyllotactic pattern of secondary floral meristems is evident, with younger meristems closer to the center. (B) *clavata3-2* mutant inflorescence apex, at somewhat lower magnification than A. The developing flowers surround a clearly visible shoot apical meristem, which is extremely enlarged relative to wild type. Extra floral organs are evident in the more mature flowers, especially extra sepals and carpels.

peat receptor kinase that resembles the CLV1 protein but that is of unknown function in the plant. KAPP also interacts with the kinase domain of the CLV1 protein, as shown by the in vitro association of the kinase interaction domain of KAPP with the CLAVATA1 kinase domain produced in and purified from an *E. coli* expression sys-

tem (Williams et al. 1997). Furthermore, KAPP acts as a phosphatase that removes phosphate from the phosphoserine of the CLV1 kinase domain. If phosphorylated CLV1 protein is the active form (as indicated by the loss-of-function phenotype of kinase domain amino acid substitutions; Clark et al. 1997), and KAPP dephosphorylates CLV1 in vivo, then a plant overexpressing KAPP should show a *clv1* mutant phenotype (Fig. 3). We have overexpressed KAPP from a constitutive promoter, and the transgenic plants do indeed have a weak *clv1* phenotype, with increased carpel number in the flowers (Williams et al. 1997).

One additional gene also may code for a further component of the CLV1 pathway, the product of the *Arabidopsis* gene *WUSCHEL* (*WUS*; Laux et al. 1996). *wus* loss-of-function mutations have a phenotype opposite that of *clv1* mutants. Rather than an increase in meristem

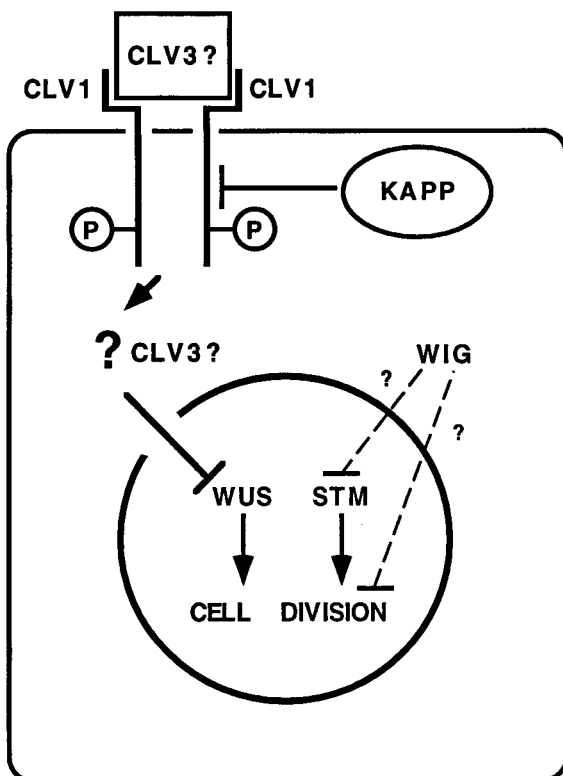


Figure 3. One possible model for the CLAVATA1 pathway and for the parallel pathway for cell division control that involves STM and WIG. CLV1 is a transmembrane receptor kinase, phosphorylated on serine. CLV3 could be the ligand or it could be an element that acts downstream from CLV1—it is shown in both positions, followed by a question mark. KAPP is a phosphatase that dephosphorylates CLV1; because CLV1 acts as a repressor of cell division, KAPP is thus formally an activator of cell division. WUS is the most downstream element in this hypothetical CLV1 pathway; because its loss-of-function phenotype is reduced cell division, it is shown as repressed by active CLV1, and as an activator of cell division. STM, a homeodomain protein, acts in the nucleus as an activator of cell division, but in a pathway not under the direct control of CLV1 (as indicated by the double-mutant experiments described in the text). WIG is a repressor of cell division that acts independently of CLV1/CLV3/WUS, perhaps through repression of STM or perhaps independently of STM.

size and cell number, there is a decrease. In *wus* embryos, the SAM is not recognizable. After germination, the region of the meristem is flattened rather than domed as in wild type, and only after weeks are any leaves formed. Following this late leaf formation, the apex stops growing; much later in the plant's life, adventitious meristems apparently form, as ectopic leaves and shoots emerge from various regions. Just as in the primary growth region, these adventitious meristems then stop their growth. On rare occasion, inflorescence meristems and a small number of flowers are formed; the flowers lack central organs. This again is opposite of the *clv1* mutant phenotype, which includes extra central organs and extra whorls of carpels. Although several interpretations for the wild-type action of WUS are possible, one is that WUS is required for there to be sufficient cell division in the SAM and in floral meristems, and therefore that WUS acts oppositely of CLV1 in shoot and floral meristems. If WUS acts downstream from CLV1, and CLV1 either represses WUS gene expression or decreases WUS protein activity (perhaps via a kinase cascade), one would expect *wus* mutations to be epistatic to *clv1* mutations. They are (Laux et al. 1996). WUS may therefore fit into the CLV1 pathway as shown in Figure 3, as a protein negatively regulated by CLV1 when CLV1 is in the activated state.

There is another *Arabidopsis* gene with a mutant phenotype very similar or identical to that of *wus*, called *SHOOT MERISTEMLESS*, or *STM* (Barton and Poethig 1993; Clark et al. 1996; Long et al. 1996; Endrizzi et al. 1996). Just as for WUS, *STM* acts opposite to the CLV genes: The wild-type function of the CLV genes is to repress cell division in meristems, whereas *STM* and WUS serve to activate meristematic cell division and are necessary for SAM initiation as well as maintenance. That *STM* is required for both processes is indicated by the meristem initiation phenotype of strong mutant alleles (*stm-1*, Barton and Poethig 1993) and the maintenance phenotype of weak alleles (*stm-2*, Clark et al. 1996). The STM protein is a member of the homeobox family, and STM RNA is found in all layers of *Arabidopsis* SAMs (Long et al. 1996). The interactions of *stm* mutations with *clv1* and *clv3* mutations are not at all the same as those of *wus* and the *clv* alleles. *clv1* and *clv3* mutations partially suppress *stm-1* and *stm-2* phenotypes and are capable of acting as dominant suppressors, despite their generally recessive character. In addition, although *stm* mutations are recessive, *stm* serves as a dominant suppressor of *clv* homozygous phenotypes. *clv stm* double mutants are intermediate between the singly homozygous plants, having more meristematic growth than *stm* alone, but less than in *clv* homozygotes. Thus, unlike *wus* mutations, *stm* mutations are not epistatic to *clv1* or *clv3* (Clark et al. 1996). One explanation for this is that STM and the CLV proteins act in separate pathways that lead to the same endpoint, a cell division decision. The expression patterns indicate that they could be acting in this fashion in the same cells, although the broader expression domain of STM indicates that it may also have activities in cells that do not express CLV1. One interpretation of the action of STM in cells that also express CLV1 is shown in Figure 3.

Given that STM seems to act in a pathway parallel (although perhaps cross-regulating) to that of CLV1, CLV3, KAPP, and WUS in the rib meristem cells, one can ask if there are any mutations among those collected with excess-cell phenotypes that might act in this parallel path. The one such gene that has been analyzed sufficiently to tell is *WIGGUM*, the mutant phenotype of which is a modest increase in floral organ number, correlated with increased cell number in early floral meristems (Running 1997). In this respect, *wig* mutants resemble *clv1* and *clv3* mutants. *wig* mutations do not act similarly to the *clv* mutants in tests of genetic interaction, however. *wig clv1* and *wig clv3* double mutants have a phenotype much more extreme than *wig* or *clv* single mutants, with massive overgrowth of the SAM and extreme disruption of floral meristems, including sometimes complete loss of determinacy (Running 1997). The SAM phenotype of the double mutants is striking, as the SAM produces undifferentiated, callus-like tissue and can achieve a diameter of more than 1 cm by the end of the plant's life. This is approximately 100 times the diameter of a wild-type SAM, indicating as much as a million-fold increase in volume in the double-mutant SAMs, as compared with wild-type. One interpretation of these results is that WIG acts to repress meristematic cell division in a separate but parallel and partly redundant pathway to CLV1 and CLV3. Eliminating any one of the pathways causes a modest increase in SAM cell number, whereas eliminating both causes SAM cell division to be completely unregulated. This interpretation is shown in Figure 3. It is not yet known if WIG acts through STM (i.e., if *stm* mutations are epistatic to *wig* mutations); thus, WIG is shown as acting independently of STM, although future experiments may indicate that WIG and STM define, together, a single pathway of cell division control. Furthermore, because the product of the WIG gene is unknown, it is not known if WIG is a cell surface receptor, ligand, element in a signal transduction pathway, or nuclear effector of cell division. Indeed, WIG could act in a different population of cells than CLV1, with loss of cell division control in two adjacent, communicating populations of cells causing a complete loss of cell division repression in the meristem.

All of the known mutant phenotypes and genetic interactions of CLV1, CLV3, STM, WIG, and WUS, and the known molecular properties and overexpression phenotype of KAPP, can be fit into the speculative model for cell division control shown in Figure 3. This model, even if true, would hold only for the cells in which CLV1, KAPP, STM, and so forth are known to be active. The only cells in which the CLV1, KAPP, and STM RNAs are found together are in those roughly coincident with the rib meristem of the SAM and a comparable region of developing floral meristems. Cells, for example, in the peripheral zone of the shoot meristem, which do not have detectable CLV1 RNA, would have to be controlled by a different set of gene products. It could be though that each meristematic zone has its own equivalent of CLV1 acting as a receptor for cell division information from nearby cells and also its own mechanism for producing a ligand for the receptors found in adjacent cells. If so, then vari-

ants of the pathway shown in Figure 3 might exist in each population of dividing cells in plants, and each population would be controlled by different ligands secreted by different sets of neighbors. Such a mechanism may account for the overall coordination of the cell divisions that occur in meristems and thus may account for the ability of meristems to maintain populations of stem cells, and at the same time produce lateral organs and additional meristems, all without substantially changing their shape, size, and clonal layering.

One scheme by which each set of meristematic cells might respond to different ligands would be for each to have a cell surface receptor like CLV1, but with an altered extracellular domain. It is already known that there is a leucine-rich repeat receptor kinase family in plants: In *Arabidopsis*, the first member of the family found was TMK1 (Chang et al. 1992), followed by RLK5 (Walker 1993) and TMKL1 (Valon et al. 1993). Mutants are not known for any of these genes, nor has any study of their expression patterns been done, so their functions in plants are unknown. Additional LRR-kinase genes in *Arabidopsis* include *ERECTA* (Torii et al. 1996), which has a mutant phenotype of shorter stems and fruits than wild type. Whether this is due to reduced cell division or to a reduction in cell elongation has not been established, but it is possible that ER, like CLV1, acts in the regulation (although positive, not negative, regulation) of cell division in particular plant regions. There are numerous additional LRRs and kinase domains related to CLV1 in the *Arabidopsis*-expressed sequence tag database. Few of the entered sequences are long enough to include the whole protein-coding region of the sequenced cDNA, so it is not known how many of these sequences code for LRR transmembrane receptor kinases, and how many for other LRR proteins or for different types of kinases. Nonetheless, the LRR receptor kinase family in *Arabidopsis* has at least four well-characterized members, and there could be dozens more.

To get a better idea of the number and expression pattern of CLV1-related genes in the *Arabidopsis* genome, we have used the part of the CLV1 gene that codes for the kinase domain as a labeled probe for screens of an *Arabidopsis* genomic bacteriophage λ library (R.W. Williams and E.M. Meyerowitz, unpubl.). Genes for several additional and previously unknown LRR kinases were found, and preliminary in situ hybridization results indicate that they have a variety of expression patterns, with some showing expression in specific subdomains of the SAM and some expressed in different domains of the floral meristem. It is thus true that there are numerous LRR kinases in *Arabidopsis* and that at least some of them are expressed in SAMs and floral meristems, as if they might indeed serve as sensors to help cells in different meristematic regions assess their environments. It may be that each functional and clonal region of shoot and floral meristems has its own set of kinases, and secretes its own set of ligands when dividing or elongating, and that by this sort of intercommunication, the coordinated cell division activities of the meristems are controlled.

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